

Message

From: Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]
Sent: 8/14/2018 3:47:25 PM
To: Harvey Clewell [HClewell@ramboll.com]; Jerry Campbell [JCampbell@ramboll.com]
CC: Robinan Gentry [rgentry@ramboll.com]; Allison Franzen [AFranzen@ramboll.com]; Miyoung Yoon [myoon@toxstrategies.com]; Sonja Sax [SSax@ramboll.com]; cvanlandingham@ramboll.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usereda39e51]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]
Subject: RE: transmission of PBPK model for chloroprene

P.S. There are three "Andersen et al. (1987)" papers on PBPK modeling. Do you mean the one on methylene chloride? And there are at least a few "Clewell et al. (2001)" papers, so I'll need to know the right one of those to check for the human QPC.

I checked both Yang et al. (2012) and Himmelstein et al. (2004) to see if those cited it, but not... I do note that for both of those papers the V/Q in humans was equal to one (QCC = QPC)!

-Paul

From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Monday, August 13, 2018 4:54 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>; cvanlandingham@ramboll.com; Vandenberg, John <Vandenberg.John@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: transmission of PBPK model for chloroprene

Hi Paul

The value of QCC for the mouse in the chloroprene model (QCC=30), is similar to the mouse value (QCC=28) in the PBPK model of Andersen et al. (1987) that was used by EPA in the IRIS assessment for methylene chloride, and is consistent with the physiology of ventilation and perfusion.

I was a member of the ILSI RSI committee that resulted in the publication of Brown et al. (1997), and the question of the correct value of QCC to use in a PBPK model for the mouse was a point of discussion at that time. As mentioned in the section beginning on p.453 of Brown et al., while the value of cardiac output used in the PBPK model of Andersen et al. (1987) for the rat is in agreement with the experimental measurements reported in Table 22, the value for the mouse is about double the reported values. The decision to use the higher value of QCC in the mouse was made by Mel Andersen and I when we were at Wright-Patterson AFB, and was the result of comparisons of PBPK models with data for a number of chemicals.

If you convert the alveolar ventilation rates in Table 31 to the same units as the cardiac output in Table 22 (mL/min), the experimental value of 14 mL/min for a 23-30g mouse that is reported in Table 22 of Brown et al. is inconsistent with the experimental value for the ventilation rate in the mouse in Table 31, and would result in a mismatch between ventilation and perfusion (V/Q ratio). Apart from situations involving strenuous activity or disease, ventilation and

perfusion rates are maintained at a V/Q ratio close to 1, and a departure from this value by more than 20% is considered of clinical significance. While the data from rats and dogs are consistent with a V/Q ratio close to unity, the mouse data are not.

Species	Alveolar Ventilation (mL/min/100g) (Table 31)	BW (g)	Alveolar Ventilation (mL/min)	Cardiac Output mL/min (table 22)	V/Q ratio
Mouse	116.5	30	35	14	2.50
Rat	52.9	250	132	110	1.20
Dog	23.1	15000	3465	2936	1.18

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From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]

Sent: Monday, August 13, 2018 9:41 AM

To: Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>

Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon

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Subject: RE: transmission of PBPK model for chloroprene

Jerry, Harvey,

Cc: Also including EPA colleagues, managers

The attached goes on to describe a couple of discrepancies/issues for the physiological parameters, for the most part minor. However, there is a major issue with the QCC for the mouse:

“... for the mouse the QCC and BW yield a total cardiac output of 36 ml/min, while Table 22 of Brown et al. (1997) gives a mean of 14 ml/min, with a range of 12-16 ml/min. Hence the QCC is unrealistically high, should be $\sim 11.7 \text{ L/h/kg}^{0.75}$. But using QCC=11.7 in the female_mouse_in vivo_3.R script results in significant over-prediction of the blood concentration data. This indicates a failure in in-vitro to in-vivo extrapolation, since the increase in QCC effectively increases the rate of metabolism (when flow-limited) to a similar extent. At a minimum, the “parallelogram” approach suggests that a similar correction, a factor of 2.6 times the mean, should be applied for the human QCC when calculating human internal doses.”

It's possible that there's a mistake in the in-vitro to in-vivo metabolic extrapolation/calculations that you all can correct. But I flicked through that part of the 'documentation' spreadsheet and see that the calcs are embedded, so I expect all of those check out. What's written above re. a parallelogram option is just my take for possibly dealing with the discrepancy, but we'd need to have an internal discussion about that before determining if it's acceptable.

Also, please provide the full citation for “Clewell et al. (2001)”, listed for human physiological parameters. And as indicated before, the spreadsheet refers to another sheet for calculation of the partition coefficients, which wasn't included.

Best regards,
-Paul

From: Jerry Campbell [<mailto:JCampbell@ramboll.com>]
Sent: Monday, August 06, 2018 9:30 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; cvanlandingham@ramboll.com; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <ssax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I was just getting to that option. See if this will work.

Jerry Campbell
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From: Schlosser, Paul [<mailto:Schlosser.Paul@epa.gov>]
Sent: Monday, August 06, 2018 9:26 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <ssax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Try just changing the file-extension from .zip to .txt and sending as an attachment. I'm trying to unzip the thing from the sharepoint site and just getting a spinning wheel.

From: Cynthia Van Landingham [<mailto:cvanlandingham@ramboll.com>]
Sent: Monday, August 06, 2018 9:19 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <ssax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Unfortunately, I believe that the restrictions are on your end not ours. We can all see the files no problem.

Cynthia

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From: Schlosser, Paul [<mailto:Schlosser.Paul@epa.gov>]
Sent: Monday, August 06, 2018 8:18 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <ssax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I tried to just download it. Does it have to be this complicated? We'll be sharing with everyone as part of our open and transparent process...

-Paul

From: Cynthia Van Landingham [<mailto:cvanlandingham@ramboll.com>]
Sent: Monday, August 06, 2018 9:13 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
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Subject: RE: transmission of PBPK model for chloroprene

Paul,
Did you download the zip file to your hard drive and then open or did you open it on the OneDrive site? If you did not try this, selecting all the files and allowing OneDrive to produce one download zip may be best. The chloroprene_model.o_error.txt file is not in the zip we created so may be something that is being created due to the download process. Please read that file to find out if your IT security set-up is preventing files from being extracted.

Thanks, Cynthia

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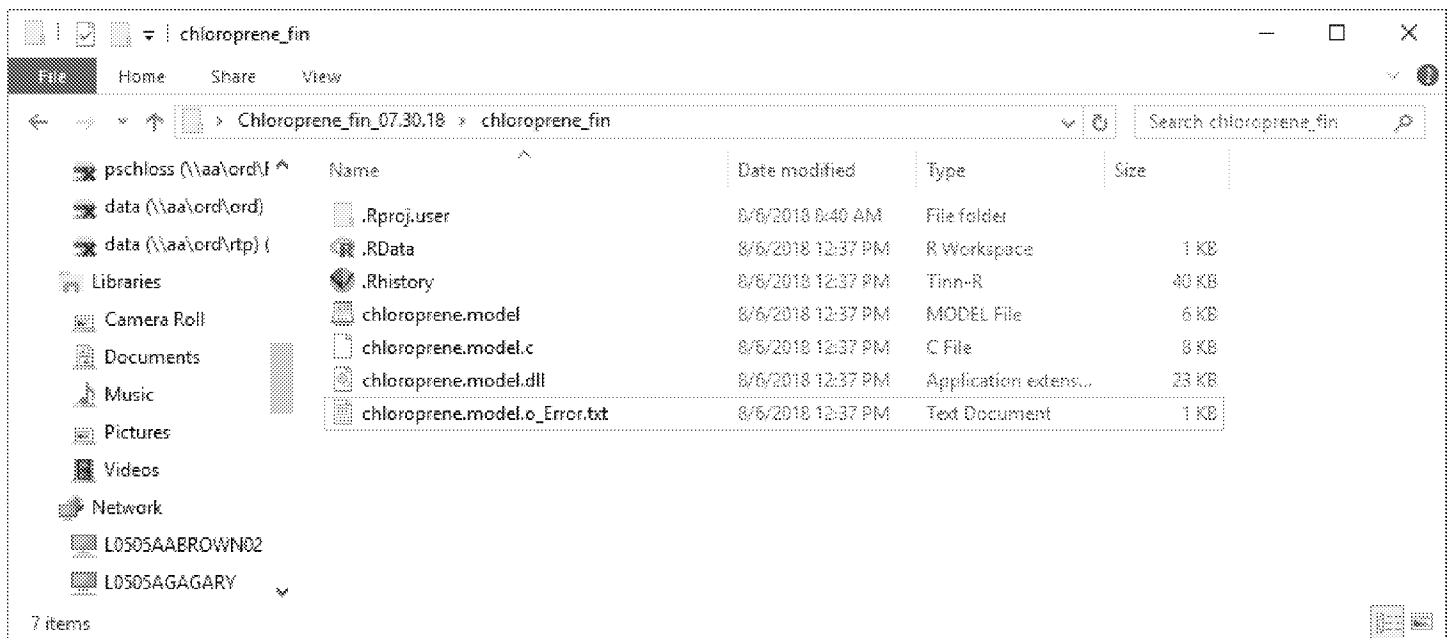
From: Schlosser, Paul [<mailto:Schlosser.Paul@epa.gov>]
Sent: Monday, August 06, 2018 7:53 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <ssax@ramboll.com>
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Harvey,

I sent a separate email to Alison. Below is a screenshot of the model folder that I got. There are none of the scripts listed in the Excel 'documentation' file.

Once we have those, give us some time to look at it. Hopefully it's easy enough to figure out, but we can let you and Jerry know if we need a walk-through.

-Paul



From: Harvey Clewell [mailto:HClewell@ramboll.com]

Sent: Friday, August 03, 2018 2:02 PM

To: Schlosser, Paul <Schlosser.Paul@epa.gov>

Cc: Robinan Gentry <rgentry@ramboll.com>; cvanlandingham@ramboll.com; Allison Franzen

<AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>;

Sonja Sax <SSax@ramboll.com>

Subject: transmission of PBPK model for chloroprene

Hi Paul



As promised, we are providing you with the PBPK model for chloroprene written in R, with all the associated scripts and documentation. You should have received a separate email with an invitation to access the files on Microsoft OneDrive. Please let me if you have any problem downloading or opening them. Jerry Campbell would be happy to come over to EPA to help you set up the run environment in R studio and answer any questions you may have about running the model.

I'm looking forward to talking with you about the model and discussing any questions, suggestions, or concerns regarding it. Would it be possible to arrange an initial meeting sometime in the next few weeks. Miyoung Yoon is completing her review of the metabolism parameter scaling approach and I would like to be able to include you in the discussion of her recommendations.

Harvey Clewell

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